

Exhibit A:
Copy of Lab Notebook LB137
pages 1-13

AIM- Formulation calculations for Budesonide concentrated suspensions of differing Budesonide and Polysorbate 80 content.

~~The concentrated suspensions are to be manufactured according to Development Protocol D. M.P. [REDACTED]~~

The Formulation of Budesonide Inhalation Suspension is given in Report R117.

Budesonide Ph. Eur	0.5mg/ml
Polysorbate 80 Ph. Eur	0.2mg/ml
Sodium Chloride Ph. Eur	8.5mg/ml
Sodium Citrate Dihydrate Ph. Eur	0.5mg/ml
Citric Acid Monohydrate Ph. Eur	0.28mg/ml
Disodium Edetate Dihydrate Ph. Eur	0.1mg/ml
Water for Injections	2ml Fill volume

Concentrated Budesonide Suspension (A)

- needs to have a Budesonide concentration of 37.5 mg/mL
- needs to have a Polysorbate 80 content of 5% of the total which will be present upon dilution with placebo to form the final product suspension (as detailed in R117)
- all other excipients should be the same concentration as in the final product suspension (as stated in R117)

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To make up the final product suspension from (A), would have to dilute by a factor of:

$$\frac{37.5}{0.5} = 75 \quad \begin{array}{l} \text{(Budesonide conc in A)} \\ \text{(Budesonide conc in final product suspension)} \end{array}$$

$$\frac{\text{Polysorbate 80 content of (A)}}{\text{Polysorbate 80 content of final product}} = \text{Dilution factor} \times \frac{5}{100}$$

(the 5/100 is due to needing 5% of Polysorbate 80 content of final product suspension in (A))

$$\begin{aligned} \text{Therefore, Polysorbate 80 content of (A)} &= 0.2 \times 75 \times \frac{5}{100} \\ &= 0.75 \text{ mg/mL} \end{aligned}$$

Concentrated Budesonide Suspension (B)

- the same as (A) but with a Budesonide concentration of 75 mg/mL

Dilution factor to make up final product suspension from (B)

$$\begin{aligned} &= \frac{75}{0.5} = 150 \end{aligned}$$

$$\begin{aligned} \text{Polysorbate 80 content of (B)} &= 0.2 \times 150 \times \frac{5}{100} \\ &= 1.50 \text{ mg/mL} \end{aligned}$$

Author signature

Date

Reviewer signature

Date

Witnessed and understood by

Date

Concentrated Budesonide Suspension ©

- needs to have a Budesonide concentration of 75 mg/mL
- needs to have a Polysorbate 80 content of 100% of the total which will be present upon dilution with placebo to form the final product suspension (with formulation as stated in R117)
- all other excipients should be the same concentration as in the final product suspension

Dilution factor to make up the final product suspension from ©

$$= \frac{75}{0.5} = 150$$

Therefore, the Polysorbate 80 content of © = $0.2 \times 150 \times 10$
 $= 30 \text{ mg/mL}$

Concentrated Budesonide Suspension ①

- the same as © but with a Budesonide concentration of 150 mg/mL

Dilution factor to make up the final product suspension from ①

$$= \frac{150}{0.5} = 300$$

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Therefore, the Polysorbate 80 content of ① = $0.2 \times 300 \times 100$
 $= 60 \text{ mg/mL}$

Based on the calculations above, the Formulations of the concentrated Budesonide suspensions ①, ②, ③ and ④ are as stated in Table 1 below.

Table 1 - Formulations of Concentrated Budesonide Suspensions.

	Concentration (mg/mL)	
Budesonide	A	37.5
	B	75
	C	75
	D	150
Polysorbate 80 Ph. Eur	A	0.75
	B	1.50
	C	30
	D	60
Sodium Chloride Ph. Eur	A, B, C, D	8.5
Sodium Citrate Dihydrate Ph. Eur	A, B, C, D	0.5
Citric Acid Monohydrate Ph. Eur	A, B, C, D	0.28
Sodium Edetate Dihydrate Ph. Eur	A, B, C, D	0.1
Water for Injections	A, B, C, D	to 1 mL

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Formulation of placebo required to dilute (A) to form a final product suspension with the formulation stated in R117

Polysorbate 80 concentration in (A) = 0.75 mg/mL

Polysorbate 80 concentration in final product suspension = 0.20 mg/mL

Polysorbate 80 concentration in placebo required for dilution = x mg/mL

→ From LB137 p2, dilution factor = 75

→ Polysorbate 80 = Polysorbate 80 + Polysorbate 80

(1) content of final product suspension contents of (A) content of placebo

→ Content = concentration \times volume

Therefore, using equation (1)

$$(75 \times 0.2) = (1 \times 0.75) + (74 \times x)$$

$$x = \frac{(75 \times 0.2) - (1 \times 0.75)}{74}$$

$$= 0.1926 \text{ mg/mL}$$

Formulation of placebo required to dilute (B) to form a final product suspension with the formulation stated in R117

Polysorbate 80 concentration in (B) = 1.50 mg/mL

From LB137 p2, dilution factor = 150

Therefore, using equation ①

$$\begin{aligned} \text{Polysorbate 80} &= \frac{(150 \times 0.2) - (1 \times 1.5)}{149} \\ \text{concentration in} & \\ \text{placebo needed} & \\ \text{to dilute ③} & \\ &= 0.1913 \text{ mg/mL} \end{aligned}$$

For ③ and ④, 100% of the Polysorbate 80 present in the final product suspension upon dilution is present in ③ and ④. Therefore, no Polysorbate 80 is present in the placebo used for dilution.

The formulations of the placebo batches required to dilute ③, ④, ⑤ and ⑥ to form product suspensions as stated in R117 are detailed in Table 2 below.

Table 2.

	Concentration (mg/mL)	
Polysorbate 80 Ph. Eur	A	0.1926
	B	0.1913
	C	0
	D	0
Sodium Chloride Ph. Eur	A, B, C, D	8.5
Sodium Citrate Dihydrate Ph. Eur	A, B, C, D	0.5
Citric Acid Monohydrate Ph. Eur	A, B, C, D	0.28
Sodium Edetate Dihydrate Ph. Eur	A, B, C, D	0.1
Water for Injections	A, B, C, D	to 1mL

Author signature

Date

Reviewer signature

Date

Witnessed and understood by

Date

M. P. H. 1

P. H. A.

M. P. H. 1

TO STUDY THE EFFECT OF STERILISATION

Aim: To manufacture 4 concentrates with varying concentrations of Polyorbate 80 and Budesonide, for autoclaving and then assaying for chemical degradation.

	Budesonide	Polyorbate 80
• Conc. A	37.5mg/ml 18.75g for 500ml batch	0.75mg/ml 0.375g for 500ml batch
• Conc. B	75mg/ml 37.5g for 500ml batch	0.15mg/ml 0.075g for 500ml batch
• Conc. C	75mg/ml 37.5g for 500ml batch	30mg/ml 15g for 500ml batch
• Conc. D	150mg/ml 75g for 500ml batch	60mg/ml 30g for 500ml batch

Equipment:

- Balance - Sartorius AC210 S 110 NR: 000866W
- Magnetic Stirrer
- Silverson LR4 Mixer

Samples: Budesonide Placebo without Polyorbate 80.
Batch: LB087 P185

METHOD:

1. In a 600ml beaker, weigh out the correct amount of Polyorbate
2. Add 500ml of Placebo ex: LB087 P185
3. Mix using a magnetic stirrer for 10 minutes.
4. Portion 100-200ml of the mixture into another beaker for the final flush of the silverson head.
5. Place under the silverson mixer the remaining solution and add Budesonide slowly until the Budesonide has completely been homogenised.
6. Homogenise for 10 minutes after all the Budesonide has been added.
7. Flush the silverson head with the remaining placebo mixture (leaving batch in 500ml).

8. Mix under the magnetic stirrer for 15 minutes to allow for all the foam to disappear.
9. Add the concentrate to a 500 mL volumetric flask and make to volume with the remaining 50 mL of placebo.
10. Remove any air bubbles that have foamed on the top of the suspension by blowing it with air.

L6157 P9

10:04:07

N 0.0000 g

N + 0.3763 g

CONCENTRATE A
TWEEN 80 BN: 4001

N 0.0000 g

N + 0.7518 g

CONCENTRATE B
TWEEN 80 BN: 4001

N + 0.0000 g

N + 15.0045 g

CONCENTRATE C
TWEEN 80 BN: 4001

N - 0.0001 g

N - 0.0001 g

N 0.0000 g

N + 30.0023 g

CONCENTRATE D
TWEEN 80 BN: 4001

N 0.0000 g

N + 18.8450 g

N + 0.0115 g

CONCENTRATE A
SOL DE MEXICO BRIDGEMORE
BN: 6260103A-0m

N 0.0000 g

N + 37.5972 g

N + 0.0261 g

CONCENTRATE B
BRIDGEMORE

N 0.0000 g

N + 37.5641 g

N + 0.0150 g

CONCENTRATE C
BRIDGEMORE

N 0.0000 g

N + 75.0978 g

N + 0.0172 g

CONCENTRATE D
BRIDGEMOREWeights for Tween 80 and
Bridgeland for the Concentrates
A, B, C and D.BRIDGEMORE
Conc A. = 18.8335g

Conc B. = 37.5711g

Conc C. = 37.5491g

Conc D. = 75.0806g

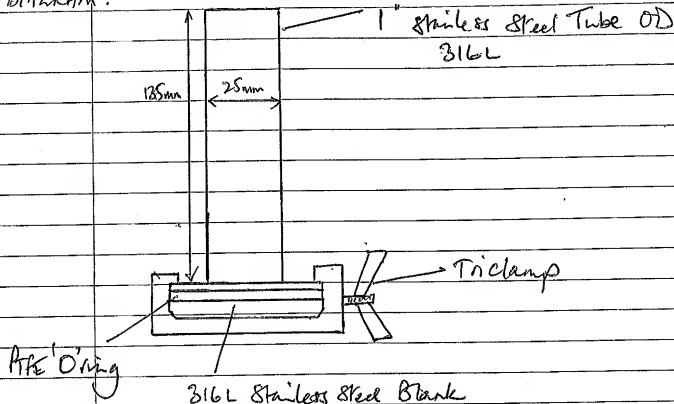
Time taken for homogenizing using the
Silverson LR4

	START	END	TOTAL TIME
Conc A	11.00	11.40	40 minutes
Conc. B	12.00	12.40	40 minutes
Conc. C	14.00	14.27	27 minutes
Conc. D	14.40	15.10	30 minutes

Aim:

Describe the type of vessel to be used in the heat sterilisation study for Budesonide Concentrate.

Diagram.



- NOTE:
- All stainless steel is 316L
 - All tubes have been passivated.
 - Manufactured by MJD Engineering.

AIM: To autoclave the Budesonide Concentrates at various temperatures and times in stainless steel vessels as detailed on LB137 P10.

SAMPLES:	Budesonide Concentrates	Budesonide	Polypropylene 80
	Conc. A	37.5mg/ml	0.75mg/ml
	Conc. B	75mg/ml	1.5mg/ml
	Conc. C	75mg/ml	30mg/ml
	Conc. D.	150mg/ml	60mg/ml

Equipment: LTE Vacuum Autoclave S/N: J3063 (located in the microbiology lab at Goddard Road).

8x Stainless steel vessels

SAMPLES	AUTOClave HOLDING Temp	AUTOClave HOLDING TIME
A1/A2	Control	Control
A3/A4	110°C	120 mins
A5/A6	121°C	20 mins
A7/A8	121°C	30 mins
B1/B2	Control	Control
B3/B4	110°C	120 mins
B5/B6	121°C	20 mins
B7/B8	121°C	30 mins
C1/C2	Control	Control
C3/C4	121°C	20 mins
D1/D2	Control	Control
D3/D4	121°C	20 mins

[illegible]

LB187
P12

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121°C for 30 mins.

File is	Size	or use
Final c	11	Ballast air
Drivins-	-	None
Precool	-	Ballast air
Printin	16	- 1.8 m
Stop re	6	- 119.0 °C
Start r	17	- 119.0 °C
Load fa	-	- 119.0 °C
Safe lc	-	90.0 °C
Holdins	-	2.1 m
Pursins	-	-
Purse r	-	-
Steril	-	-
CLE 6	-	-

Cycle 6

121°C for 20 mins

Final
Drawing

CYCLES

110°C for 60 mins.
But cycled Thrice

CYCLES N°1

SIGNATURE

Cycle completed..... 13142143

CYCLE PASS

12131115	66.2	100.0	2.110
12130140	60.0	100.4	2.150
12129140	71.4	105.0	2.125
12128140	75.0	105.4	2.068
12127140	81.2	110.0	2.150
12126140	86.2	110.6	2.000
12125140	96.0	111.2	2.175
12124140	106.4	111.0	2.160
12123140	112.0	111.0	1.515
12122140	112.2	111.0	1.545
12121140	111.2	111.0	1.475
12120140	111.6	111.0	1.495
12119140	112.0	111.0	1.520
12118140	111.6	111.0	1.575
12117140	111.4	111.0	1.405
12116140	112.0	111.0	1.510
12115140	112.2	111.0	1.545
12114140	111.2	111.0	1.470
12113140	111.6	111.0	1.495
12112140	112.0	111.0	1.525
12111140	111.6	111.0	1.600
12101140	111.2	111.0	1.475
12091140	111.6	111.0	1.490
12081140	112.0	111.0	1.510
12071140	112.2	111.0	1.555
12061140	111.2	111.0	1.475
12051140	111.0	111.0	1.495
12041140	112.2	111.0	1.530
12031140	111.2	111.0	1.520
12021140	111.4	111.0	1.400
12011140	112.0	111.0	1.510
12001140	112.2	111.0	1.550
11591140	111.2	111.0	1.470
11581140	111.0	111.0	1.500
11571140	112.2	111.0	1.525
11561140	111.2	111.0	1.540
11551140	111.6	111.0	1.405
11541140	112.0	111.0	1.520
11531140	111.2	111.0	1.540
11521140	111.6	111.0	1.405
11511140	112.0	111.0	1.520
11501140	111.4	111.0	1.525
11491140	111.4	111.0	1.400
11481140	112.2	111.0	1.515
11471140	111.4	111.0	1.570
11461140	111.6	111.0	1.405
11451140	112.2	111.0	1.525
11441140	111.2	111.0	1.475
11431140	111.0	111.0	1.500
11421140	112.0	111.0	1.560
11411140	111.4	111.0	1.475
11401140	112.2	111.0	1.520
11391140	111.2	111.0	1.495

CYCLES N°2

SIGNATURE

Cycle completed..... 16134120

CYCLE PASS

15122100	65.2	100.0	2.095
15122100	67.2	100.4	2.120
15121100	70.0	105.0	2.000
15120100	75.2	105.6	2.200
15119100	80.0	110.0	2.130
15118100	87.0	110.6	2.075
15117100	97.0	111.2	2.195
15116100	106.4	111.0	2.200
15115100	111.0	111.0	1.515
15114100	112.0	111.0	1.540
15113100	111.2	111.0	1.490
15112100	111.6	111.0	1.500
15111100	112.0	111.0	1.525
15110100	112.0	111.0	1.570
15109100	111.2	111.0	1.405
15108100	111.6	111.0	1.505
15107100	112.2	111.0	1.535
15106100	111.4	111.0	1.560
15105100	111.4	111.0	1.490
15104100	111.0	111.0	1.510
15103100	112.2	111.0	1.540
15102100	111.0	111.0	1.500
15101100	111.4	111.0	1.495
15091100	111.0	111.0	1.515
15081100	112.2	111.0	1.545
15071100	111.0	111.0	1.490
15061100	111.6	111.0	1.495
15051100	112.0	111.0	1.565
15041100	111.4	111.0	1.480
15031100	111.0	111.0	1.505
15021100	112.2	111.0	1.530
15011100	111.2	111.0	1.505
14991100	111.6	111.0	1.490
14981100	112.0	111.0	1.520
14971100	111.6	111.0	1.590
14961100	111.4	111.0	1.480
14951100	112.0	111.0	1.510
14941100	112.2	111.0	1.560
14931100	111.2	111.0	1.470
14921100	111.6	111.0	1.495
14911100	112.0	111.0	1.535
14901100	111.2	111.0	1.470
14891100	111.0	111.0	1.500
14881100	111.2	111.0	1.470
14871100	111.0	111.0	1.500
14861100	112.2	111.0	1.540
14851100	111.6	111.0	1.470
14841100	111.0	111.0	1.530
14831100	112.2	111.0	1.560
14821100	111.2	111.0	1.545
14811100	111.4	111.0	1.475
14801100	112.0	111.0	1.545
14791100	111.2	111.0	1.475
14781100	111.0	111.0	1.505
14771100	112.0	111.0	1.575

CYCLE 5.

N°1 cycled first

then N°2 cycled after.

N°1 + N°2 = 120 min

110°C for
60 min +
60 min.

NOTE These are
prints of a bottle
of water (1L) inside
an autoclave that
contains a temperature
probe. This probe
shows the temperature
of the inside of the
autoclave. Hence
this is equivalent to
the temperature of the
suspension in the
stainless steel vessels